Quality of Life Trajectories in Epilepsy: A review of the literature

Ann Jacoby[1] and Gus A. Baker[2]

[1] Division of Public Health, University of Liverpool, UK; [2] Division of Neurosciences, University of Liverpool, UK

Address for correspondence:

Ann Jacoby, PhD
Division of Public Health
University of Liverpool
Whelan Building (3rd Floor)
The Quadrangle
Brownlow Hill
Liverpool
L69 3GB
UK

ajacoby@liv.ac.uk

Word Count: 9,258

Key Words: quality of life; adults; trajectory; clinical course; new-onset seizures; surgery; remission; intractability

Abstract

The potential psychosocial sequelae of epilepsy are well-documented, but it cannot be assumed that trajectories for quality of life (QOL) of people with epilepsy will inevitably follow its clinical course. In this paper, we draw on available literature to suggest likely QOL trajectories associated with epilepsy and the broad range of disease-, patient- and other-focussed factors that appear important in determining them. We conclude that both the likely shape and timeframe for QOL trajectories associated with particular clinical scenarios can be delineated; but that their shape can be altered by a much wider range of factors than those represented as epilepsy disease progression. We identify contributory factors currently relatively unexplored and highlight implications for treatment and areas for future research.

Word Count: 120

Background

Epilepsy is a generally benign clinical condition with a high likelihood of remission [1,2]. Around six percent of the general population will experience at least one seizure during the course of their lifetime [3], but many of them will never have a second [4], the risk of doing so decreasing with increasing time from the initial event [5]. Evidence from the small number of studies that have examined it suggest that antiepileptic drug (AED) treatment has little impact on the short or longer term likelihood of recurrence following a single seizure [6,7]. However, once an individual experiences a second seizure, treatment with AEDs becomes the norm as they then fulfil the commonly accepted (if arbitrary [8]) criterion for a diagnosis of epilepsy. In treated patients the likelihood of a remission of seizures is high, estimated at between 65% and 80%, though better for generalised than for partial epilepsies [4]. In those patients in whom remission is prolonged, withdrawal of AEDs is generally considered, though the largest study to consider the outcomes of AED withdrawal put the risk of relapse in those doing so as twice that of those remaining on treatment [9]. Around 20-30% of patients treated for epilepsy will fail to respond to treatment and will continue to have seizures: and only around 20% of these patients will have even short-lived seizure-free periods [4]. Many such patients will then wish to consider surgery for their condition, in the hope that removal of affected brain tissue will render them seizure free: and a review of the outcomes of surgical treatment worldwide shows that success rates are, indeed, high for most surgical procedures [10]. The various clinical trajectories described here are illustrated in Figure 1.

Life expectancy is known to be reduced in people who develop seizures [11,12,13], with reductions being highest at the time of diagnosis. Sander and Sillanpaa [4] note that mortality rates are highest among people under 40 years, a group that has the lowest mortality risk in the general population. Rates are highest among those with generalised seizures and symptomatic epilepsy [14]. Epilepsy has a known association with increased risk of suicide, particularly shortly after diagnosis [15]. Deaths from accident and trauma are also more common than in the general population. Accident rates are increased in people with epilepsy (PWE) compared to the general population, though the increase is a modest one [16]. PWE are also at increased risk of suffering from other chronic conditions of ill-health [17,18]. In addition to these increased mortality and physical morbidity risks, epilepsy has well-documented psychosocial sequelae – and it is these and their implications for overall quality of life (QOL) that are the focus of this paper.

One thing that is clear from available research evidence is that PWE as a group have poorer QOL than people without epilepsy [17,19,20,21]. For example, Strine et al [17] compared health-related QOL in a very large community sample of adults with and without seizures identified via the US National Health Interview Survey; and reported that, after adjustment for socio-demographic characteristics, those with seizures were more likely to experience psychological distress, sleep impairment, and pain; were more likely to be suffering serious mental illness; and were also more likely to be physically inactive and to have co-morbidities. They were also less likely to be married and in employment currently. A similar, earlier study in Canada drew on the 1990 Ontario Health Survey and involved a large representative sample of the population of Ontario Province [19]. QOL was significantly poorer for those identifying themselves as having epilepsy than for either those with a chronic illness other than epilepsy or those who described themselves as healthy. Social participation indices were also significantly lower for PWE, as was participation in regular physical activity. Finally, PWE had lower annual income than their comparator groups and reported more disability days annually.

Useful though such studies are, by treating all those reporting seizures as a single group, they tend to paint a grimmer picture than is necessarily suggested by research in which different groups of PWE are differentiated. Yet, as is pointed out by Wilson et al [22], for an individual patient developing seizures such differentiation is important and may help alert them and involved health professionals as to likely responses and requirements for intervention. Responses and interventions in this context will not only be clinical but also psychosocial, aimed not only at managing seizures but also at maximising QOL. It cannot be assumed that the trajectories for quality of life of PWE will *de facto* reflect its clinical trajectories; and elucidation of likely QOL trajectories and the wide range of factors contributing to them is therefore important.

Within sociological studies of health and illness, the term ‘trajectory’ has been used to describe the course and timescale of events associated with phenomena such as dying, or the onset of a chronic illness [23]. In its original application, it was used to describe the efforts made by patients, their families and their professional carers to control the clinical course of chronic illness, prevent or manage its symptoms, live with any associated disabilities, and hence maintain good quality of life [24]. The trajectory framework has been applied to consideration of a range of chronic

conditions, including cancer [25], diabetes [26], heart disease [27], multiple sclerosis [28,29] and stroke [30,31], though not, to our knowledge, epilepsy. In this paper, we utilise the term 'trajectory' not strictly as proposed by Corbin and Strauss, but for elucidation of the QOL course and timescale of QOL events resulting from developing seizures and epilepsy. We draw both on our own research into QOL in epilepsy and other available literature to suggest likely QOL trajectories associated with epilepsy and the broad range of disease-, patient- and other-focussed factors that appear important in determining them. We also attempt to identify possible factors currently relatively unexplored and to highlight areas for future research.

Within the trajectory framework proposed by Corbin and Strauss, they delineate eight distinct phases typically seen in chronic illnesses (Box 1) the first six of which, we suggest, are applicable to the clinical course of epilepsy. Since Corbin and Strauss developed the framework in the context of the care of dying patients, the final two phases, 'downward' and 'dying' are less relevant; and it has been argued that the framework should also include a 'recovery' phase [32], since many chronic illnesses do not end in death and may even involve stabilisation at original levels of functioning and quality of life. In this paper, we will provide evidence of just such a likely trajectory for epilepsy and of the likely timescales involved. Acknowledging the limitations of their framework in this respect [33], its authors recognise that new health technologies can alter illness trajectories significantly. In the context of epilepsy, surgery represents an increasingly important technology and we will highlight the significant contribution it can have in altering QOL trajectories of those undergoing it.

As highlighted in Box 1, the concept of an illness trajectory involves evolution over time; and tracking it therefore requires data that are longitudinal and preferably long-term. For obvious reasons of complexity and costs, relatively few longitudinal QOL studies have been conducted in epilepsy and many of those that have follow their protagonists for relatively short periods of time only. As a result, much of the data drawn upon here derives from cross-sectional descriptive studies, involving specific epilepsy sub-populations (e.g. those with 'active' epilepsy, or those undergoing surgery) which, taken together, suggest certain likely trajectories for patients falling within a particular subgroup. However, there are also some longitudinal studies which have followed cohorts of PWE from the time of onset of their seizures over more extensive periods of time to explore subsequent QOL outcomes. Some of these studies involve adults with epilepsy whose seizures commenced in adulthood, others

adults with epilepsy that commenced in childhood. Some studies have involved PWE only, while others have compared QOL in PWE with QOL in non-epileptic controls – either persons with other chronic conditions of ill-health, or healthy individuals, or both.

Whether the source is cross-sectional or longitudinal, there are some significant limitations with the data available and with their interpretation. First, the numbers of patients involved in these studies are often quite small; and in the longitudinal studies, loss to follow-up means that the survivors may be those with either the *most* or *least* benign QOL trajectories - it may be the case that patients whose epilepsy impacts most on QOL feel least able to devote time to participation in research; conversely, those whose epilepsy has minimal QOL impacts may come to view such research as irrelevant to them, and so may abandon participation. Second, definitions of QOL are often unspecified and there may be questions about the ecological validity of both the definitions and the measures used to operationalize them, given potential variation in the importance of different QOL domains across different cultural groups. Third, even when comparing studies conducted in the same cultural setting, variation in the measures used to assess QOL makes comparison of findings sometimes less than satisfactory; likewise, in the published longitudinal studies, length of follow-up varies from as little as 12 months to as much as 30 years. Furthermore, many of the longitudinal studies involve only short-term follow-up, despite the fact that, as pointed out by Wilson et al [22,34] the processes involved are likely to be long-term. A further problem, specific to cross-sectional studies, is that they can demonstrate associations between hypothesised predictor variables and QOL outcomes, but cannot establish causal effects or the pin-pointing of key points in the QOL trajectory. Finally, virtually all studies exploring QOL outcomes in PWE are quantitative in nature, allowing definition of the size of the problem of poor outcomes, but with limited ability to shed light on the processes involved. Despite these limitations, we can begin to piece together a picture of the different QOL trajectories associated with having epilepsy, and it is to this that we now turn.

Search Strategy and Selection Criteria

References for this review were identified by conducting electronic searches of the following databases: Allied and Complementary Medicine (1985 onwards), British Nursing Index (1994 onwards), CINAHL (1982 onwards), MEDLINE (1966 onwards),

Science Direct (1995 onwards), and The Cochrane Library (2007). Subject search terms and combinations included: epilepsy, chronic illness or chronic disease and quality of life or health and quality of life, or trajectory or illness trajectory or quality of life trajectory, or outcomes and prognosis, or remission induction, or sickness impact profile. The search was limited to adults (19 years and over) and only papers published in English were reviewed. References were also identified from relevant articles and through searches of the authors' own files. The search is current up to October 2007.

Findings

Impact of a single or few seizures on QOL

Given the threatened losses that the onset of seizures poses (including loss of employment, loss of the right to drive, loss of sense of control, loss of sense of self), it would be surprising if these were not reflected in some way in the QOL profiles of those individuals who experience them. Velissaris et al [35] conducted a phenomenological study using in-depth, semi-structured interviews to explore the psychological impact of a first seizure (in the Corbin & Strauss model, the trajectory onset) and noted that persons thus affected typically reported shock and fear at what had happened, anxieties about the possibility of seizures recurring, an increased sense of vulnerability and limitations on their social activities - reactions which collectively represented loss of control. In some patients this sense of lost control was pervasive, in others it was fairly limited; but by three months patients in both groups were reporting largely normal psychological functioning and those in the group experiencing pervasive loss of control were also reporting an improved sense of self.

Dworetzky et al [36] compared quantitatively QOL of 30 adults experiencing a single seizure (PSS) with that of 29 adults with well-controlled epilepsy (PWC) and with 24 adults recently diagnosed as having hypertension (PHT) – and likewise concluded that having a single seizure has only a modest impact on QOL. All three groups of patients completed the SF-36 health status measure [37], as well as questions about the perceived impact of their condition, medication status and health care utilisation. At baseline interview, no significant differences were found between the three groups for any of the eight domains of the SF-36, for QOL overall, or for the perceived

impact of their condition on QOL. However, PSS reported significantly higher use of healthcare services than did either of the two other groups; and this high usage continued through the year of follow-up perhaps, the authors suggest, because of the need to monitor responses to new medication taking. When their scores on the SF-36 were compared with age-adjusted population norms, PSS had significantly lower scores on the energy/vitality and physical role functioning domains, but their scores on the other six domains were comparable – despite the fact that over a third (38%) of PSS, when asked at follow-up, considered that their seizure had had a moderate to extreme impact on their QOL.

Jacoby et al [38,39] reported 2-year QOL outcomes in patients with single or few seizures recruited to a randomised trial of opposing policies for management of single or few seizures. The policies in question were immediate treatment with AED medication or treatment deferred until such time as either the patient or the treating clinician deemed it necessary; and all patients were tracked for clinical outcomes for a minimum of one year. At the same time, they were asked to complete QOL questionnaires at the point of randomisation and two and four years subsequently. The results of the treatment comparison have been reported in detail [7] and are not the point of interest here – suffice it to say that in the long term pursuing a policy of immediate treatment offered no clinical advantage. Likewise, there were no QOL advantages of immediate treatment, with the single exception of driving status, where the advantage was for those treated immediately. Of considerable relevance, however, was the finding that the QOL profile of patients reporting a single seizure only at randomisation was significantly better than that of patients reporting more than one seizure [38]. And though overall rates of employment at point of randomisation were lower than for the general UK population, those experiencing a single pre-randomisation seizure were around twice as likely to be in employment at that time point as were individuals experiencing two or three, and three times as likely as those experiencing four or more [40]: by four year follow-up employment rates for those having had a single seizure only were approaching UK norms. Furthermore, disregarding the number of seizures pre-randomisation, patients who remained seizure-free following randomisation had much enhanced QOL profiles at 2-year follow-up compared to their counterparts with continuing seizures [39]. Taken together then, these findings support the conclusion that patients having a single or few seizures only will experience relatively few and relatively short-lived decrements to QOL.

Finally, Lindsten et al [41,42] examined 10-year QOL outcomes in a cohort of individuals 17 years and over experiencing newly diagnosed unprovoked seizures (27% of whom had experienced only a single seizure) and their sex- and age-matched controls. They reported that across the 10-year period, most leisure-time activities, marital and driving status were unaffected by the onset of epilepsy; and the negative effects that were noted (for physical activity, travelling abroad and overall activity) occurred later rather than earlier in follow-up, suggesting that factors other than seizures were the cause. The authors suggest a possible link between reduced leisure activity and the finding that PWE also reported reduced income compared to controls, and higher morbidity. However, they also note that in their cohort, PWE had significantly lower income levels than controls *before* the index seizure. Employment rates were similar for PWE and controls across the 10-year period and did not evolve negatively among PWE after the onset of their seizures (though there were differences between those who became seizure-free compared to those with continuing seizures). Thus, these authors too present a generally optimistic picture of the likely QOL trajectory of patients experiencing a single or few seizures, concluding that important QOL effects will be present only for those whose seizures do not remit.

In summary, *then, for persons experiencing a single or few seizures only, the trajectory suggested by the available evidence is one of a sudden dip in QOL immediately following the seizure event, followed by a fairly quick return (generally suggested as somewhere between 1 and 2 years) to (almost) normal functioning (when compared to the general population) and a life quality comparable to that which preceded the event (Figure 2).*

QOL in patients with active epilepsy

Patients with active epilepsy are represented in the model by Corbin and Strauss as being in the acute phase of the chronic illness trajectory. Definitions of ‘active’ epilepsy vary across reported studies from seizures in the last two years [43] to seizures in the last three months [20], hampering direct comparison of findings. Nonetheless, seizure frequency has been heavily implicated in QOL across all these studies [20,43,44,45,46,47] and there is evidence too of a role for seizure recency. Baker et al [44] reported findings from a European-wide study involving over 5,000 PWE, in which active epilepsy was defined as seizures in the previous 12 months (it is worth noting that around 95% of these individuals were also taking AEDs). There

was a clear linear trend for QOL, with informants reporting at least one seizure per month in the previous year also reporting greatest impact of their epilepsy on daily functioning and scoring lowest on all eight SF-36 domains, and those experiencing no seizures in the last year reporting the least impact and scoring highest. Leidy et al [45] studied QOL in 139 adults with active epilepsy, defined as seizures and/or AEDs in the last year, recruited from three US epilepsy centres. Though the authors did not comment on it, this appeared to be a fairly disabled group of PWE, with only 35% reporting being in full-time employment despite a mean age of 38.5 years. The comparison made was between patients who were seizure-free in the previous four weeks, those having had between 1-5 seizures in that time period and those having had six or more. Patients experiencing six or more seizures had significantly poorer QOL, as measured by the SF-36 health status measure, than those experiencing 1-5, who in turn reported poorer QOL than the seizure-free patients. In a multivariate model, seizure frequency, though not seizure recency, was associated with significantly poorer QOL. Leidy et al comment that while the meaning of any reduction in the number of seizures to patients themselves has still to be defined, the QOL differences detected in their study between patients experiencing 1-5 or 6 or more recent seizures are substantial, such that reducing seizure frequency by only a few, 'could have a dramatic impact'. In a large US survey, Kobau et al [20] defined active epilepsy as either taking AEDs or experiencing seizures in the last three months; and reported a role both for seizure frequency and seizure recency in this group. Thus, 56% of those with active epilepsy reported only fair or poor health status, but the percentage rose to 75% in those who had had at least one seizure in the preceding three months. Adults with recent seizures also reported more physically unhealthy days, compared to those with active epilepsy but no recent seizures.

In summary, *all the available evidence suggests that having active epilepsy negatively and sometimes profoundly depresses QOL profiles; the subsequent QOL trajectory will be then influenced by whether the epilepsy remains active, progresses or remits, as will be shown below. As will also be shown below, factors other than the clinical will also bear upon these QOL trajectories (Figure 2).*

QOL in patients with intractable seizures

Studies focussing on patients with intractable epilepsy (the unstable phase in the Corbin and Strauss model) emphasise that in this subgroup potential QOL impacts are substantial [48,49,50,51,52]. Baker et al [48] showed for example, that compared to patients whose seizures were in remission, patients with intractable seizures scored significantly worse across all domains of the Nottingham Health Profile [53], as well as in relation to sense of mastery and self-esteem. Likewise, in the study by Vickrey et al [49] of 340 adults with refractory partial seizures evaluated pre-surgically, QOLIE-89 [54] domain scores were considerably lower than has been reported for patients with well-controlled seizures, ranging from 43.6 for the epilepsy-related domain to 47.5 for the mental health domain. Perhaps unsurprisingly, in both these studies, seizure frequency emerged as less important than patient perceived seizure severity in predicting QOL. In Vickrey's study, for example, correlations of QOLIE scores with seizure frequency were all non-significant, whereas those with seizure severity were significant even though modest (ranging from -0.17 to -0.29). The seizure severity item most highly correlated with QOLIE scores was post-seizure recovery time, with worse QOL associated with longer recovery time. Greater seizure severity was also negatively correlated with better employment status. These findings have led the two sets of authors – and, most recently, Harden et al [52] - to argue that in this particular subgroup of PWE, QOL improvements may be attainable simply by reducing the severity of seizures [52,55] and that the role of recovery time for QOL in patients with refractory epilepsy requires further elucidation [49]. Further confirmation for the minor role played by seizure frequency in the face of intractable epilepsy comes from Szaflarski et al [51]. The primary focus of their investigation was the effects of age-related factors on QOL in patients with drug-resistant epilepsy, but they also explored the effects of other epilepsy-related factors and mood. These authors did not consider the role of seizure severity in their analysis, but as in the studies already discussed, seizure frequency was found not to correlate with QOL.

One likely reason for the lack of importance of seizure frequency in all these studies is highlighted by the work of Birbeck et al [56], who showed that in this group of highly disabled patients, reduction in the number of seizures did not translate into meaningful QOL improvements except where complete seizure freedom was achieved.

In summary*, we would suggest that the QOL trajectory of patients with intractable seizures will likely be subject to a series of peaks and troughs, with a range of factors other than seizure frequency determining its precise shape (Figure 2). Certainly,*

current evidence supports that QOL is substantially compromised by having intractable epilepsy; and for the small number of individuals who experience brief periods of seizure freedom, the disappointment and demoralisation when seizures recur may cause a major dip in QOL. The most likely scenario being the absence of any significant reduction in the number of seizures, reducing the perceived severity of those seizures may lead to an upturn in the QOL trajectory.

QOL in patients undergoing surgery

Perhaps because of the very large potential costs and benefits, the QOL outcomes of surgery for epilepsy have been much examined [22,34,57-77]. Most authors report QOL improvements: for example, Markand et al [67] found significant QOL increments, at one- and two-year follow-up, for surgically compared to medically managed patients, on 10 of the 17 domains of the QOLIE-89. There is, however, ongoing debate as to the nature of relationship between clinical and QOL outcomes of surgery. Several authors [65,66,73] conclude that there is a post-surgical QOL continuum, whereby QOL is highest for patients rendered seizure-free or experiencing auras only and lowest for patients whose seizures are reduced in frequency by less than 75%. Other authors characterise QOL improvements post-surgically as having a clear 'cut-off' point, which differentiates between those patients who attain complete seizure freedom and the rest [67].

Whichever of these definitions ultimately prevails, the available data suggest that 'successful' surgery can profoundly effect for the better QOL of those undergoing it and that QOL improvements can be sustained long-term [57, 59,63,65,69,76]. Spenser et al [72] followed a large cohort of patients undergoing surgery in whom they assessed QOL, using the QOLIE-89 measure, at intervals up to five years. QOL improved substantially across all outcome groups in the immediate post-operative period, then declined in those patients whose seizures persisted till it reached pre-surgical levels. In contrast, QOL continued to improve in those remaining seizure-free, with improvements levelling off at around two years when a QOL 'ceiling' appeared to be reached. Furthermore, this study and the one reported by Mikati et al [68] suggest that QOL can improve to the point of normalisation within a relatively short timeframe. In the former, the QOL scores observed for PWE at two-year follow-up were similar to those observed for the general population on seven of the eight SF-36 scales (the exception being for social functioning). In the latter, the authors demonstrated that by three-year follow-up, QOL of patients undergoing temporal

lobectomy did not differ significantly from healthy controls – a finding they attribute not only to the high level of surgical success (85% of patients became seizure-free), but also to factors such as the high level of social and family support offered. While in broad agreement with these conclusions, Markand et al [67] note that QOL improvements may be delayed in some domains compared to others.

The broad message, then, seems to be that where it results in good seizure control surgery promotes good QOL and shifts people into a 'recovery' phase in terms of chronic illness trajectories [32]. There are, however, some important caveats to this general rule. Langfitt et al [64] report that QOL may actually worsen after surgery among a group of patients they refer to as 'double losers' (ie. where persistent seizures were accompanied by post-operative decrements in memory function). Von Lehe et al [73] report that even patients achieving good seizure control experience only modest benefits when the outcomes addressed relate to objective socio-economic status rather than subjective life quality. Post-surgical QOL has been shown to be predicted by pre-surgical QOL independent of seizure status [77], a finding paralleled in studies of the outcome of drug therapy {39,78,79]. Furthermore, patients' pre-surgical expectations for QOL post-surgically are important determinants of their perceptions of its success [74]; and Wilson et al [75] have reported what they refer to as a paradox of cure, namely that patients may report QOL decrements despite clinical improvements post-surgically because of the difficulties faced in reconceptualising their personal identity as one without epilepsy [34] and the resultant the 'burden of normality'. Nonetheless, the message from their work is in agreement with the one proposed by others cited above, in that despite initial difficulties in adjusting to life without seizures, adjustment trajectories for the majority of operated patients culminated in 'psychosocial success' by the time of two year review [22].

In summary*, the QOL trajectory varies post-surgery largely in line with clinical outcome. Surgery is followed immediately by an upturn in the trajectory, which is gradually reversed if the clinical outcome is poor; the upturn continues for some time where the clinical outcome is good, though the 'burden of normality' may mean the shape of the curve is not necessarily a smooth one; the trajectory levels off at around two to three years after surgery (Figure 2).*

QOL in patients seizure-free and in remission

Epidemiological studies highlight that patients with epilepsy in remission (variously defined as seizure-free for one or two years) constitute the largest group of PWE, (between 60-70% of all patients); and the collective message from studies of QOL in adults is that remission of seizures following pharmacological treatment, like successful surgery, is associated with the recovery phase of the chronic illness trajectory and a return to near-normal functioning [80,81,82,83,84]. For example, in Jacoby's study [80] of 607 persons living in the UK, three-quarters of whom were in a remission of at least two years, dysfunction as measured by the six domains of the Nottingham Health Profile (energy, pain, emotion, sleep, social isolation, physical mobility) was minimal; and only small percentages were concerned about their epilepsy, felt stigmatised by it, or felt socially restricted by it. Furthermore, there was little evidence of social activity being reduced and employment rates were near those of the normal UK population. In the Norwegian study reported by Stavem et al [81], 70% of those taking part were seizure-free in the previous year; and their SF-36 scores were close to the normal population. Raty et al [84] reported on young adults specifically (aged 18-27 years) with uncomplicated epilepsy (ie. without any associated neurological impairment) and concluded that their condition affected their QOL 'to only a small degree'. Finally, though in the study by Leidy et al [45] the focus was on seizure frequency in the last month, it is worth noting that for those classified as seizure-free the median time since their last seizure was 365 days (compared to 6.5 and 1.5 days in the other two groups): the finding that SF-36 domain and summary scale (mental and physical health) scores for seizure-free patients were similar to those for the general US population is therefore unsurprising in light of findings from these other studies. Hessen et al [83] suggest an important role for neuropsychological function in determination of the QOL trajectory for patients who attain seizure freedom: these authors found that in adults seizure-free for at least two years, neuropsychological function was in the normal range, and educational and employment status were also similar to the general population mean.

One interesting finding from the UK community study reported by Jacoby et al [43] was that though there were marked differences in QOL between patients experiencing seizures and those seizure-free in the year prior to study, increasing length of seizure freedom beyond this was not associated with increasing QOL – the relationship appeared to be a dichotomous rather than a linear one. Thus there were no significant differences in the percentages reporting anxiety, depression or felt

stigma, or currently in employment when those reporting periods of seizure freedom of 2-4 years, 5-9 years and 10 or more years were compared. One explanation for this finding suggested by the authors is that the sample studied included a large percentage of PWE who had opted to remain on AED therapy despite long periods of remission; and continuing AED treatment has been shown to have adverse effects on psychosocial outcomes [85,86]. In Jacoby's study, these individuals may therefore have had a poorer QOL profile than would individuals with a remote history of seizures who had opted to withdraw from AEDs and so were not eligible for inclusion.

A challenge to the broad conclusion from the above literature that seizure freedom equates to good QOL comes from the recently published study by Kobau et al [20], wherein individuals with a history of seizures, however distant, reported impaired life quality. For example, 47% of those with a history of epilepsy reported fair or poor health status compared to only 20% of those without such a history; they also reported around double the number of physically and mentally unhealthy days and activity limitation days. This may however, simply reflect that the definition of 'active' in this study was a much narrower one (seizures and/or AEDs in the last three months) than that employed in other studies focussing on remission. Though on a much smaller scale, the study by Argyriou et al [87] supports the findings of Kobau et al, with no reduction in psychological function as measured by presence of anxiety or depression, but clear reductions in physical and social function, when persons with uncomplicated, well-controlled epilepsy were compared to healthy controls. The authors of this latter study attribute the negative QOL outcomes they document to stigma, a point we return to below, as well as to lack of epilepsy services and the repercussions of such for assessment, management and awareness in the rural area in which their work was conducted.

In summary, *the evidence suggests an upward trajectory for remission - albeit following a more prolonged period of QOL disruption than for those experiencing only single or few seizures - leading to near-normal functioning. Again, two years appears to be a critical cut point for QOL improvements* (Figure 2).

Role of other epilepsy variables

Generally speaking, the observed associations between QOL and other epilepsy-related variables are weaker than those between QOL and seizure activity [72].

Jacoby et al [43] examined the effects of current seizure activity, seizure type, aetiology, age at onset and duration of epilepsy in a multivariate analysis: current seizure activity explained most variation in QOL function and was the only clinical variable predicting perceived impact of epilepsy and personal fulfilment scores; age and onset and duration were important in explaining depression scores; age of onset was also important in relation to felt stigma scores. There was some evidence that seizure type was associated with employment status, a finding reported elsewhere in the literature [88,89,90]. Timing of seizures has been suggested as important for QOL [47], perhaps because of the threats daytime seizures pose to safety, but also to the concealability of epilepsy and avoidance of stigma – a point we return to below.

In contrast to the relative unimportance of these epilepsy variables, the literature increasingly points to an important role for adverse effects of AED treatment [47,91,92,93] in depressing QOL of those taking them; and of the potential for QOL increments if AEDs can be withdrawn [94]. Boylan et al [92] express concern that an over-enthusiastic focus on treating seizures pharmacologically may actually reduce QOL by increasing the risk of AED-related depression (the role of which we return to below). Reduction of AED adverse effects is likely therefore to lead to an upturn in the QOL trajectory, even where no other changes in clinical status occur.

Role of non-epilepsy factors in determining QOL trajectories

Non-epilepsy factors identified as contributing to QOL among PWE fall into two broad categories: those that further increase vulnerability to impaired QOL and a downward trajectory; and those appearing to promote resilience (ie. an individual's capacity to overcome adversity) and enhanced QOL, even in the face of important clinical factors. A substantially greater body of work to date has addressed the former than the latter; for which reason we consider them first.

Psychiatric co-morbidity: A rapidly expanding literature addresses the major contribution psychiatric factors, particularly anxiety and depression, make to perceived QOL of PWE [47,92,95,96,97,98,99,100,101,102,103,104]. The prevalence of both disorders is high in PWE, estimated as between 10-25% for anxiety [105] and between 10-60% for depression [106]. In a large sample of adults completing the 2004 US Healthstyles Survey [101], those self-reporting epilepsy

were twice as likely to self-report anxiety or depression in the previous year than those without epilepsy and those with active epilepsy (defined as seizures in the last three months or on AED medication) were three times more likely. Reduced QOL among PWE with depression, compared to PWE who are depression-free, is commonly reported [98,100,104]. Zeber and colleagues found QOLIE-89 scores to be significantly reduced by comorbid depression for all types of seizures [104]. A number of authors [99,100,107] provide evidence to suggest that clinical and socio-demographic factors play only modest roles in determining QOL of PWE, while depression primarily, but also anxiety and seizure concerns exert powerful independent effects, explaining most of the variance in QOL scores. In line with this finding, Attarian et al [108] found no relationship between seizure intractability and severity of depression, which was as prevalent in patients seizure-free for six months or longer as in patients who experiencing continuing seizures. Boylan et al [92] note that in their study of patients with refractory epilepsy, depression was common, severe, under-diagnosed, largely untreated and a powerful determinant of QOL, whereas seizure-related factors were not. So strong was the association between depression and QOL in the study by Tracy et al [107] that its authors posit that, 'any therapeutic intervention observed to improve 'quality of life' . . . must at least consider the possibility that the outcome is strongly related to alteration in mood, not betterment of the underlying neurological or medical condition.'

Other co-morbidities: Related to psychiatric morbidity, links have been shown between QOL and neuropsychological function generically [109], memory function specifically [95], sleep disturbance [110,111] and fatigue [47]. Additionally, medical co-morbidities have been shown to be more common in PWE [17,18] and also linked to impaired QOL [45,58,112]. Pulsipher et al [112] report that increased number of co-morbid conditions was associated with decreased QOL, and that co-morbid medical and psychiatric conditions together accounted for almost 14% of the variance in QOL scores. The number of co-morbid psychiatric conditions better predicted scores for psychosocial satisfaction, epilepsy related effects and cognition; whereas the number of co-morbid medical conditions better predicted role limitations and physical performance.

Stigma: Finally, there are almost certainly important social context effects [113] and a role for stigma in determining the shape of QOL trajectories in epilepsy [114,115,116]. For example, Jacoby [117] showed that people whose epilepsy was in remission rarely reported feeling stigmatised: but those who did were more likely to

report anxiety about epilepsy, had reduced scores for mastery and self-esteem, poorer psychological function, and more future-oriented uncertainty. Likewise, Baker et al [118] in a European-wide study involving over 5000 patients with epilepsy reported that high scores on a stigma scale were correlated with worry, negative feelings about life, long-term health problems, injuries, and reported side effects of AEDs. Stigma perception also contributed significantly to QOL in the study by Suurmeijer et al [119], alongside psychological distress and loneliness. These non-clinical factors appeared to act as mediators of the effects of clinical variables such as seizure frequency. DiIorio et al [120] note that perceived stigma is associated with decreased self-efficacy among PWE, perhaps creating a vicious circle of negative effects wherein poor self-efficacy leads to poor self-management of epilepsy and so to increasing disease severity and increasing stigma.

Cerebral reserve: With regard to QOL promoters, research has highlighted a role for what can broadly be referred to as aspects of 'resilience'. For example, Oyegbile et al [121] highlight the role of 'cerebral reserve' (as indicated by higher educational level and/or occupational attainment and/or increased participation in mindful activities) in modifying cognitive morbidity in PWE. They showed that though degree of generalised cognitive impairment – a major contributor to disease burden - was associated with duration of epilepsy, the association was attenuated by having more years of formal education (and, indeed, ceased to be significant). The authors suggest that years of education may, in fact, be a marker 'for those who, at the outset of the disorder, are on different trajectories' with regard to educational attainment and lifespan cognition – and, by implication, QOL. Other studies reporting educational level as a predictor of QOL in adults include those by Loring et al [100] and Pulsipher et al [112]. Wakamoto et al [122] examined long-term outcomes in individuals with childhood-onset epilepsy now aged 20 years and older; and concluded that where patients were of normal intelligence the prognosis was favourable.

Self-efficacy and social support: Self-efficacy and mastery have been suggested as important for good QOL [80, 120,123,124,125], as has having access to good social support [123,125]. In the study by Amir et al [123], the group of interest was patients with chronic, intractable epilepsy: and unsurprisingly the more severe their epilepsy, the more impaired their life quality. However, the negative effects of disease severity were mediated by having a high sense of control. There was also a strong association between disease severity and levels of social support and between levels of social support and QOL – the authors argue that social support can be seen as, 'a

mirror image of social stigma' whereby, 'the quality of the social network becomes the evidence of social rejection (or acceptance) for the individual.' They conclude that PWE do not necessarily need to see an improvement in the clinical features of their condition to see an improvement in their QOL, since this is also attainable by focussing on improvements in these other non-epilepsy related aspects of their existence.

Optimism: Other 'resilience' focussed factors examined in the literature on QOL in epilepsy are those of positive affect [124] and optimism [126]. In the study by Pais-Ribeiro et al [126], seizure frequency and severity emerged as unimportant, whereas having an optimistic orientation to their condition and a perception of their cognitive function as good were strongly predictive of PWE's physical and mental health and overall QOL. The authors suggest therefore that interventions 'with an impact on perception of cognitive function and/or epilepsy-specific optimistic orientation can have a profound effect on the lives of individuals with epilepsy'; and that patient support groups should aim to foster positive expectations of life with epilepsy among their members. Finally, though rarely referred to in the literature, the contribution of spirituality to QOL was explored by Giovagnoli et al [127], who documented significant correlations between aspects of spirituality and overall QOL (as measured by the WHO Spiritual, Religious and Personal Beliefs Scale [128] and WHOQOL 100 [128] respectively).

In summary*, then, research across a wide range of variables potentially contributing to QOL trajectories for PWE suggest a minor role for most clinical ones other than seizure activity, the obvious exception being AED effects. There is increasing evidence that the QOL trajectory will be depressed for individuals who experience psychiatric morbidity and stigma. The role of resilience, in its broadest sense, for enhancing QOL trajectories in epilepsy has yet to be fully explored; however, previous research suggests it will be important to utilise the concept of resilience as referring not simply to individual traits such as self-efficacy and spirituality, but to a process also involving external factors such as the presence or absence of social capital and support.*

Role of age of onset of epilepsy

A point that requires emphasis here is that the studies reported above relate to QOL trajectories as suggested by the literature on epilepsy developing predominantly in adulthood. Studies specifically tracking outcomes in adulthood of childhood-onset seizures present a rather different picture, with long-term and often substantial QOL deficits clearly apparent [86, 122,129,130,130,131]. In the cohort of 100 patients followed by Sillanpaa and colleagues, adult QOL across a number of domains was impaired compared to that of healthy controls, despite that their epilepsy was uncomplicated by any neurological impairment or disability. Thus, as adults these patients reported poorer physical fitness, though not self-assessed health status [132]; higher levels of co-morbidity, particularly psychiatric co-morbidity [129]; were less likely to marry and had fewer children [130]; had poorer educational level and were less likely to be in employment [131]; had lower socioeconomic status [86] and were less likely to be satisfied with their present life [131]. The authors conclude that childhood-onset epilepsy has a 'persistent long-term adverse impact' on QOL even in patients in remission [86]. An important positive finding in this otherwise fairly gloomy trajectory – and one supportive of Jacoby's findings [80] in relation to adults with epilepsy in remission - is that where patients had both entered remission *and* been able to withdraw successfully from medication, the QOL impacts were relatively modest, with no significant differences between them and their healthy controls for health, employment or socioeconomic status and low reported self-perceived impacts of their condition. The same conclusion was drawn by Shackleton et al [133], who retrospectively surveyed a cohort of patients newly diagnosed with epilepsy in childhood and adolescence, some 30 years after diagnosis. Significantly fewer of the group with epilepsy than in the general Dutch population were married and significantly more lived alone. Both educational achievement and employment status were impaired in PWE compared to the rest of the Dutch population. As in Sillanpaa's study, patients who fared best for QOL were the group who were seizure-free and no longer taking AEDs.

What can be done to promote good QOL trajectories?

Bury [134] notes that chronic illness is, 'by definition, a long-term and perhaps permanent event in a person's life', for which reason the experiences of those with chronic illness need to be placed 'within a temporal framework.' In this review, we have tried to identify studies that allow the temporal framework of epilepsy to be explored, starting with the experience of a first seizure and the initial disruption to

QOL it causes and working through the subsequent clinical scenarios and their commonly reported QOL concomitants. Analysis of the available data allows some (albeit fairly tentative) conclusions to be drawn both about the likely shape of the QOL trajectory associated with a particular clinical course for the epilepsy and to suggest some broad time frames around its execution. However, as is now clear from the literature, QOL trajectories will not inevitably mirror the clinical course of epilepsy. Their shape can be altered in highly individualistic ways by a much wider range of factors than those represented as epilepsy disease progression. Hence, they may take a downward slope, even where seizures are well-controlled, in the presence of factors such as other medical or psychiatric co-morbidity, continued treatment with AEDs, experienced stigma and discrimination or, as illustrated in relation to surgery [22] difficulties in adjusting to being well. Conversely, the slope may move upwards despite continued seizures in the presence of high levels of personal and social capital or social support; and they may, of course, reach a point of stability. As Robinson [135] notes in the context of another neurological condition, MS, 'the trajectories of the medical course, the social career and the personal narrative may be substantially different – for the reference points of the personal, social and biomedical are at variance.' If we can understand and take account of the reference points for the personal meanings PWE attach to their condition and the formal and informal social implications that accompany it in any particular social context, we can then begin to make sense of how these interact with its biomedical features to create a particular QOL trajectory – and, by extension, what the foci of interventions aimed at altering negative QOL trajectories should be.

Social scientific studies of chronic illness offer a number of concepts useful for explaining the personal impacts of a diagnosis of epilepsy. First, chronic illness has been characterised as a situation of uncertainty about aetiology, progression and severity and unpredictability of symptom manifestations within which patients face a psychological juggling act, balancing the hope of remission against the dread of regression [136]. Second, chronic illness has been conceptualised as a particular kind of disruptive life experience [24,137]: with disruption of taken-for-granted assumptions and behaviours; of the normal rules of reciprocity with others and mutual support; and of a person's life biography. Though the concept of 'biographical disruption' has been subject to criticism for its failure to address the issue of biography for illness developing in childhood and to take account of events seen as 'normal crises' [138] we consider it still a useful concept for consideration of the potential QOL impacts for adults with epilepsy. Third, chronic illness has been

highlighted as ‘a fundamental form of suffering’ characterised by loss, particularly the loss of a sense of self [24,139] but also of the body because of the associated functional limitations. The relevance of all these concepts to epilepsy is self-evident. Epilepsy is a condition of sudden onset, where the cause is often unknown, and its physical manifestation, seizures, are unpredictable. PWE hope for remission and may be prepared to tolerate unpleasant treatment side effects in order to secure it, but even those who become seizure-free are counselled that epilepsy is controllable rather than curable, and there can be no guarantee that seizures will not recur. Epilepsy is a disruptive life experience, wherein those affected may suddenly find themselves forced to confront the negative stereotypes they and significant others hold about epilepsy [140], the restrictions epilepsy and its treatment can impose on their everyday activities [141], the changing nature of their interpersonal relationships and possible increased dependence on others [115,142], and the potentially negative implications for the future. Epilepsy is also a condition of loss, wherein seizures bring sudden and total loss of bodily function and psychological losses such as reduced self-esteem or sense of mastery are commonly reported. In Bury’s [137] study of people who developed rheumatoid arthritis, the main problem they identified in light of such losses was learning to live with their condition. People developing epilepsy likewise have to learn to live with it; and it is not surprising that in the initial stages of this learning process, many experience a downward QOL trajectory.

In contrast to these somewhat negative reflections on the nature of the experience of chronic illness, the social science literature also offers a more positive take on chronic illness and its implications for QOL. Williams [143] argues that human beings are constantly engaged in a process of interpretation of the incidents and events of their daily lives, so that they can be imbued with some sense of order. Though the sense of order is thrown into disarray by the onset of chronic illness, it can, he argues, be restored by a process of ‘narrative reconstruction’ which allows them to accommodate what has happened and to ‘reconstitute and repair ruptures between body, self and world.’ This is akin to the concept of the burden of normality [75], where the clinically successful epilepsy surgery patient has to repair ruptures between the self that was with seizures and the self that is now seizure-free.

Ormel et al [144] also offer a useful framework for understanding likely QOL trajectories, grounded in Social Production Function Theory [145]. This theory assumes that people produce their own well-being by trying to optimise achievement of universal needs within the constraints they are facing. Applying it in the context of

chronic illness, Ormel and colleagues propose that at the onset of such illness, symptoms (in the case of epilepsy, seizures) and functional limitations (which in the case of epilepsy might be emotional or cognitive impairments) impair activities and increase the costs associated with achievement of life goals, leading to an immediate downturn in QOL. Substitution of alternative activities allows a subsequent upturn in the QOL trajectory, even in the face of seemingly major reductions in functional abilities. Ormel notes that the more options for substitution that are available to them, the less vulnerable people will be to the impact of the original losses; and that the breadth of such options is likely built up over the life course. This may help to explain the very different QOL trajectories seen for people whose epilepsy develops early in life compared to those where it develops later – since the former group have less time and opportunity to develop options and possibilities for substitution. The conclusion of Ormel's analysis is that addressing factors that limit the process of substitution and providing resources or enhancing the 'behavioural repertoire' that encourage it will have a beneficial effect for QOL, shifting the trajectory upwards.

As evidenced by the various studies included in this review, patients are likely to require a period of adjustment at both ends of the clinical course of epilepsy – either to starting having or to no longer having seizures. They are therefore likely to require interventions in the form of psychosocial and vocational counselling at both time points, either to learn to live with the limitations epilepsy can impose or to becoming well. Even a single seizure threatens biographical disruption and hence creates the conditions for psychological distress and fear of stigma (as was seen in the studies by Jacoby [39] and Velissaris [35]); but such disruption may be containable if no further seizures occur – hence the findings that QOL impacts of persons experiencing single seizures are fairly modest and short-term. For those less fortunate individuals whose seizures continue, the threats in terms of disruption and loss become much larger, and the implications for QOL more significant and longer-term. Examining the impact of reducing seizure frequency in such individuals, Birbeck et al [56] conclude that QOL is only really substantially improved if they achieve complete seizure freedom. It has been shown that this happy state of affairs may be attainable through drug treatment changes even in patients with apparently drug-resistant chronic epilepsy, though the success rate is relatively small [146]. Nonetheless, this finding highlights the need for clinicians to take a proactive approach to management of such patients, for whom the QOL benefits are likely substantial. Surgery also offers the possible of seizure freedom and recovery; and it

has been argued that it should be undertaken earlier rather than later in the clinical course of epilepsy, in order to maximise QOL benefits [147].

Assuming seizure freedom is not attainable by either means (and accepting the caveats around seizure freedom as necessarily equating to high QOL) we agree with Johnson et al [99] about the need for greater emphasis on the recognition and treatment of co-morbid psychopathology among PWE. We also support the suggestion by Amir et al [123], directed at resilience rather than vulnerability, of the provision of workshops to improve sense of mastery and self-efficacy. These authors comment that the secondary effect of such workshops would be to create a sense of heightened social support, another important contributor to resilience. Helde et al [148] report support and counselling, in the form of a structured nurse-led intervention, can improve QOL of patients with uncontrolled seizures, at least in the medium term. Interestingly, the timeframe chosen for assessment of effectiveness was two years, at which point QOL improvements from baseline seen in the intervention arm were not significantly different from those seen in the control arm. Since the various studies cited in this review indicate that two years is a critical point in the adjustment process, Helde's findings may simply be a reflection of an adjustment process that would have occurred even without any intervention. Nonetheless, the core elements of a brief (1-day) interactive education session, followed by ongoing telephone-based nurse contact and support, are fairly easily performed and given the QOL effects observed, it would be valuable to replicate the study to see both if and why the findings are sustainable.

As Wilson et al [22] have pointed out, attempting to define QOL trajectories for people with epilepsy is a highly complex process and one which emphasises the highly individual nature of responses to its diagnosis, treatment, control and remission and the process of adjustment. We readily acknowledge that the applicability of the trajectories we propose here is limited by resting on research relating to groups of patients rather than individuals. Nonetheless, we would argue they represent a useful framework for broadly summarising the available evidence and extrapolating certain common patterns. Many people with epilepsy will, we think, find these patterns helpful and even reassuring, while being only too well aware of their own particular life circumstances and responses. Based on currently available evidence, we conclude that QOL trajectories in epilepsy follow fairly closely its clinical course, but that they do so is not inevitable, and a wide range of factors mediate the relationship. For this reason, management of clinical symptoms at every phase of the

epilepsy process should be routinely backed by management of psychosocial difficulties. We now need further research to elicit the competing influences of the various groups of factors. In particular greater emphasis needs to be given to aspects of resilience and the ability of PWE to accept and overcome adversity and so maintain or restore a high QOL.

Acknowledgements

Our thanks go to Dee Snape, who conducted the literature searches; and Kathleen McAdam, who helped with preparation of the manuscript. This paper is based on a lecture given by AJ at the 16th International Bethel-Cleveland Clinic Epilepsy Symposium, Beilefeld, June 2005.

Box 1: Phases in the Chronic Illness Trajectory

Phase:	**Definition:**
Pre-trajectory	Before illness course begins, no signs/symptoms present
Trajectory onset	Signs/symptoms present; diagnostic period
Crisis	Life-threatening situation requiring emergency/critical care
Acute	Active illness and/or complications
Stable	Illness course/symptoms controlled by treatment regimen
Unstable	Course/symptoms not controlled
Downward	Progressive deterioration; increasing disability/symptoms
Dying	Time immediately preceding death

(Adapted from Corbin & Strauss [33])

References

1. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729-737.

2. Cockerell OC, Johnson AL, Sander JWAS, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population based study. *Epilepsia* 1997;38:31-46.

3. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. *Epilepsia* 1975;16:1-66.

4. Sander JWAS, Sillanpaa M. Natural History and Prognosis. In: J Engel JaTAP, ed. Epilepsy: A Comprehensive Textbook. Philadelphia: Lippencott-Raven, 1997, ps.69-86.

5. Sander JWAS. Some aspects of prognosis in the epilepsies: a review. *Epilepsia* 1993;34:1007-1016.

6. First Seizure Trial Group. Randomised clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic clonic seizure. *Neurology* 1993;43:478-483.

7. Marson A, Jacoby A, Kim L, Gamble C. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* 2005;365:2007-2013.

8. Hart YM, Sander JWAS, Johnson AL, Shorvon SD. National General Practice Study of Epilepsy: recurrence after first seizure. *Lancet* 1990;336:1271-1274.

9. MRC Antiepileptic Drug Withdrawal Group. A randomised study of antiepileptic drug withdrawal in patients in remission of epilepsy. *Lancet* 1991;337:1175-1180.

10. Engel J. Surgery for Seizures. *The New England Journal of Medicine* 1996;334:647-653.

11. Cockerell OC, et al. Mortality from epilepsy: results from a prospective population-based study. *Lancet* 1994;344:918-921.

12. Lindsten H, Nystrom L, Forsgren L. Mortality risk in an adult cohort with a newly diagnosed unprovoked epileptic seizure: A population-based study. *Epilepsia* 2000;41:1469-1473.

13. Gaitatzis A, Johnson AL, Chadwick DW, Shorvon SD, Sander JW. Life expectancy in people with newly diagnosed epilepsy. *Brain* 2004;127:2427-2432.

14. Hauser WA, Hesdorffer DC. Epilepsy: Frequency, Causes and Consequences. Maryland: Epilepsy Foundation of America, 1990.

15. Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. Epilepsy and risk of suicide: a population-based case-control study. *The Lancet Neurology* 2007;6:693-698.

16. Beghi E, Cornaggia C. Morbidity and Accidents in Patients with Epilepsy: Results of a European Cohort Study. *Epilepsia* 2002;43:1076-1083.

17. Strine TW, Kobau R, Chapman DP, Thurman DJ, Price P, Balluz LS. Psychological distress, comorbidities, and health behaviors among US adults with seizures: Results from the 2002 National Health Interview Survey. *Epilepsia* 2005;46:1133-1139.

18. Tellez-Zenteno JF, Matijevic S, Wiebe S. Somatic Comorbidity of Epilepsy in the General Population in Canada. *Epilepsia* 2005;46:1955-1962.

19. Wiebe S, Bellhouse DR, Fallahay C, Eliasziw M. Burden of epilepsy: The Ontario Health Survey. *Canadian Journal of Neurological Sciences* 1999;26:263-270.

20. Kobau R, Zahran H, Grant D, Thurman DJ, Price PH, Zack MM. Prevalence of Active Epilepsy and Health-Related Quality of Life among Adults with Self-Reported Epilepsy in California: California Health Interview Survey, 2003. *Epilepsia* 2007;48:1904-1913.

21. Santhouse J, Carrier C, Arya S, Fowler H, Duncan S. A comparison of self-reported quality of life between patients with epilepsy and neurocardiogenic syncope. *Epilepsia* 2007;48:1019-1022.

22. Wilson SJ, Bladin PF, Saling MM, Pattison PE. Characterizing psychosocial outcome trajectories following seizure surgery. *Epilepsy & Behavior* 2005;6:570-580.

23. Bond J, Bond S. Sociology and Health Care. An introduction for nurses and other health care professionals. Second Edition. Edinburgh: Churchill Livingstone, 1994.

24. Corbin J, Strauss A. Unending Work and Care. Managing Chronic Illness at Home. 1988.

25. Robinson L, Nuamah IF, Cooley ME, McCorkle R. A test of the fit between the Corbin and Strauss Trajectory Model and care provided to older patients after cancer surgery. *Holistic Nursing Practice* 1997;12:36-47.

26. Walker EA. Shaping the course of a marathon: using the Trajectory Framework for diabetes mellitus. *Scholarly Inquiry for Nursing Practice: An International Journal* 1991;5:235-248.

27. Hawthorne MH. Using the Trajectory Framework: reconceptualizing cardiac illness. *Scholarly Inquiry for Nursing Practice: An International Journal* 1991;5:185-195.

28. Murphy Miller C. Trajectory and empowerment theory applied to care of patients with multiple sclerosis. *J Neurosci Nurs* 1993;25:343-348.

29. Boeije HR, Duijnstee MSH, Grypdonck MHF, Pool A. Encountering the downward phase: biographical work in people with multiple sclerosis living at home. *Soc Sci Med* 2002;55:881-893.

30. Burton CR. Re-thinking stroke rehabilitation: the Corbin and Strauss chronic illness trajectory framework. *J Adv Nurs* 2000;32:595-602.

31. Kirkevold M. The unfolding illness trajectory of stroke. *Disabil Rehabil* 2002;24:887-898.

32. Dorsett DS. The trajectory of cancer recovery. *Scholarly Inquiry for Nursing Practice: An International Journal* 1991;5:175-184.

33. Corbin J. A nursing model for chronic illness management based upon the Trajectory Framework. *Scholarly Inquiry for Nursing Practice: An International Journal* 1991;5:155-174.

34. Wilson SJ, Bladin PF, Saling MM, McIntosh AM, Lawrence JA. The longitudinal course of adjustment after seizure surgery. *Seizure* 2001;10:165-172.

35. Velissaris SL, Wilson SJ, Saling MM, Newton MR, Berkovic SF. The psychological impact of a newly diagnosed seizure: Losing and restoring perceived control. *Epilepsy & Behavior* 2007;10:223-233.

36. Dworetzky BA, Hoch DB, Wagner AK, Salmanson E, Shanahan CW, Bromfield EB. The impact of a single seizure on health status and health care utilization. *Epilepsia* 2000;41:170-176.

37. Ware J. SF-36 Health Survey: Manual and Interpretation Guide. Boston MA: The Health Institute, New England Medical Centre, 1993.

38. Jacoby A, Chadwick D, Doughty J. Social consequences of epilepsy: findings from the UK MRC study of early epilepsy and single seizures. *Epilepsia* 2001;42:9.

39. Jacoby A, Gamble C, Doughty J, Marson A, Chadwick D. Quality of life outcomes of immediate or delayed treatment of early epilepsy and single seizures. *Neurology* 2007; 68:1188-1196.

40. Holland P, Lane S, Whitehead M, Marson A, Jacoby A. Labour market participation following onset of seizures and early epilepsy: findings from a UK cohort. In submission to *Epilepsia*.

41. Lindsten H, Stenlund H, Edlund C, Forsgren L. Socioeconomic prognosis after a newly diagnosed unprovoked epileptic seizure in adults: A population-based case-control study. *Epilepsia* 2002;43:1239-1250.

42. Lindsten H, Stenlund H, Forsgren L. Leisure time and social activity after a newly diagnosed unprovoked epileptic seizure in adult age. A population-based case-referent study. *Acta Neurol Scand* 2003;107:125-133.

43. Jacoby A, Baker GA, Steen N, Chadwick DW. The clinical course of epilepsy and its psychosocial correlates: findings from a UK community study. *Epilepsia* 1996;37:148-161.

44. Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. *Epilepsia* 1997;38:353-362.

45. Leidy NK, Elixhauser A, Vickrey B, Means E, Willian MK. Seizure frequency and the health-related quality of life of adults with epilepsy. *Neurology* 1999;53:162-166.

46. Djibuti M, Shakarishvilli R. Influence of clinical, demographic, and socioeconomic variables on quality of life in patients with epilepsy: Findings from Georgian study. *J Neurol Neurosurg Psychiatry* 2003;74:570.

47. Senol V, Soyuer F, Arman F, Ozturk A. Influence of fatigue, depression, and demographic, socioeconomic, and clinical variables on quality of life of patients with epilepsy. *Epilepsy & Behavior* 2007;10:96-104.

48. Baker GA, Smith DF, Dewey M, Jacoby A, Chadwick DW. The initial development of a health-related quality of life model as an outcome measure in epilepsy. *Epilepsy Research* 1993;16:65-81.

49. Vickrey BG, Berg AT, Sperling MR *et al.* Relationships between seizure severity and health-related quality of life in refractory localization-related epilepsy. *Epilepsia* 2000;41:760-764.

50. Wada K, Kawata Y, Murakami T. Sociomedical aspects of epileptic patients: Their employment and marital status. *Psychiatry and Clinical Neurosciences* 2001;55:141-146.

51. Szaflarski M, Meckler JM, Privitera MD, Szaflarski JP. Quality of life in medication-resistant epilepsy: The effects of patient's age, age at seizure onset, and disease duration. *Epilepsy & Behavior* 2006;8:547-551.

52. Harden CL, Maroof DA, Nikolov B *et al.* The effect of seizure severity on quality of life in epilepsy. *Epilepsy & Behavior* 2007;11:208-211.

53. Hunt SM, McKenna SP, Williams J. Reliability of a population survey tool for measuring perceived health problems: a study of patients with osteoarthritis. *J Epidemiol Community Health* 1981;35:297-300.

54. Devinsky O, Vickrey BG, Cramer J *et al.* Development of the quality of life in epilepsy inventory. *Epilepsia* 1995;36:1089-1104.

55. Smith DF, Baker GA, Dewey M, Jacoby A, Chadwick DW. Seizure frequency, patient perceived seizure severity and the psychosocial consequences of intractable epilepsy. *Epilepsy Res* 1991;9:231-241.

56. Birbeck GL, Hays RD, Cui XP, Vickrey BG. Seizure reduction and quality of life improvements in people with epilepsy. *Epilepsia* 2002;43:535-538.

57. Asztely F, Ekstedt G, Rydenhag B, Malmgren K. Long term follow-up of the first 70 operated adults in the Goteborg Epilepsy Surgery Series with respect to seizures, psychosocial outcome and use of antiepileptic drugs. *Journal of Neurology, Neurosurgery, and Psychiatry* 2007;78:605-609.

58. Aydemir N, Ozkara C, Canbeyli R, Tekcan A. Changes in quality of life and self-perspective related to surgery in patients with temporal lobe epilepsy. *Epilepsy & Behavior* 2004;5:735-742.

59. Bien CG, Schulze-Bonhage A, Soeder BM, Schramm J, Elger CE, Tiemeier H. Assessment of the long-term effects of epilepsy surgery with three different reference groups. *Epilepsia* 2006;47:1865-1869.

60. Cankurtaran ES, Ulug B, Saygi S, Tiryaki A, Akalan N. Psychiatric morbidity, quality of life, and disability in mesial temporal lobe epilepsy patients before and after anterior temporal lobectomy. *Epilepsy & Behavior* 2005;7:116-122.

61. Chin PS, Berg AT, Spencer SS *et al.* Patient-perceived impact of resective epilepsy surgery. *Neurology* 2006;66:1882-1887.

62. Devinsky O, Barr WB, Vickrey BG *et al.* Changes in depression and anxiety after resective surgery for epilepsy. *Neurology* 2005;65:1744-1749.

63. Jones JE, Berven NL, Ramirez T, Woodard A, Hermann BP. Long-term psychosocial outcomes of anterior temporal lobectomy. *Epilepsia* 2002;43:896-903.

64. Langfitt JT, Westerveld M, Hamberger MJ *et al.* Worsening of quality of life after epilepsy surgery - Effect of seizures and memory decline. *Neurology* 2007;68:1988-1994.

65. Lowe AJ, David E, Kilpatrick CJ *et al.* Epilepsy surgery for pathologically proven hippocampal sclerosis provides long-term seizure control and improved quality of life. *Epilepsia* 2004;45:237-242.

66. Malmgren K, Sullivan M, Ekstedt G, Kullberg G, Kumlien E. Health-related quality of life after epilepsy surgery: a Swedish multicenter study. *Epilepsia* 1997;38:830-838.

67. Markand ON, Salanova V, Whelihan E, Emsley CL. Health-related quality of life outcome in medically refractory epilepsy treated with anterior temporal lobectomy. *Epilepsia* 2000;41:749-759.

68. Mikati MA, Comair YG, Rahi A. Normalization of quality of life three years after temporal lobectomy: A controlled study. *Epilepsia* 2006;47:928-933.

69. Reid K, Herbert A, Baker GA. Epilepsy surgery: patient-perceived long-term costs and benefits. *Epilepsy & Behavior* 2004;5:81-87.

70. Selai CE, Elstner K, Trimble MR. Quality of life pre and post epilepsy surgery. *Epilepsy Res* 2000;38:67-74.

71. Spencer SS, Berg AT, Vickrey BG *et al.* Initial outcomes in the Multicenter Study of Epilepsy Surgery. *Neurology* 2003;61:1680-1685.

72. Spencer SS, Berg AT, Vickrey B *et al.* Health-related quality of life over time since resective epilepsy surgery. *Ann Neurol* 2007;62:327-334.

73. von Lehe M, Lutz M, Kral T, Schramm J, Elger CE, Clusmann H. Correlation of health-related quality of life after surgery for mesial temporal lobe epilepsy with two seizure outcome scales. *Epilepsy & Behavior* 2006;9:73-82.

74. Wilson SJ, Saling MM, Kincade P, Bladin PF. Patient expectations of temporal lobe surgery. *Epilepsia* 1998;39:167-174.

75. Wilson SJ, Bladin PF, Saling MM. Paradoxical results in the cure of chronic illness: the "burden of normality" as exemplified following seizure surgery. *Epilepsy & Behavior* 2004;5:13-21.

76. Tellez-Zenteno JF, Dhar R, Hernandez-Ronquillo L, Wiebe S. Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. *Brain* 2007;130:334-345.

77. Rose KJ, Derry PA, Wiebe S, McLachian RS. Determinants of health-related quality of life after temporal lobe epilepsy surgery. *Qual Life Res* 1996;5:395-402.

78. Marson AG, Al-Kharusi AM, Alwaidh M *et al.* The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369:1000-1015.

79. Marson AG, Al-Kharusi AM, Alwaidh M *et al.* The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369:1016-1026.

80. Jacoby A. Epilepsy and the quality of everyday life: findings from a study of people with well-controlled epilepsy. *Soc Sci Med* 1992;43:657-666.

81. Stavem K, Loge JH, Kaasa S. Health status of people with epilepsy compared with a general reference population. *Epilepsia* 2000;41:85-90.

82. Aldenkamp AP, van Donselaar CA, Flamman H, Lafarre DLW. Psychosocial reactions to the epilepsy in an unselected group of patients with epilepsy under treatment in general hospitals. *Seizure* 2003;12:101-106.

83. Hessen E, Lossius MI, Reinvang I, Gjerstad L. Predictors of neuropsychological impairment in seizure-free epilepsy patients. *Epilepsia* 2006;47:1870-1878.

84. Raty LKA, Larsson BMW. Quality of life in young adults with uncomplicated epilepsy. *Epilepsy & Behavior* 2007;10:142-147.

85. Jacoby A, Johnson AL, Chadwick DW. Psychosocial outcomes of antiepileptic drug discontinuation. *Epilepsia* 1992;33:1123-1131.

86. Sillanpaa M, Haataja L, Shinnar S. Perceived Impact of Childhood-onset epilepsy on Quality of Life as an adult. *Epilepsia* 2004;45:971-977.

87. Argyriou AA, Papapetropoulos S, Polychronopoulos P, Corcondilas M, Argyriou K, Heras P. Psychosocial effects and evaluation of the health-related quality of life in patients suffering from well-controlled epilepsy. *J Neurol* 2004;251:310-313.

88. Elwes RDC, Marshall J, Beattie A, Newman PK. Epilepsy and employment: a community based survey in an area of high unemployment. *J Neurol Neurosurg Psychiatry* 1991;54:200-203.

89. Jacoby A. Impact of epilepsy on employment status: Findings from a UK study of people with well-controlled epilepsy. *Epilepsy Res* 1995;21:125-132.

90. Collings J. Epilepsy and the Experience of Employment. A Report of a National Survey by the British Epilepsy Association. Leeds: British Epilepsy Association, 1992.

91. Jacoby, A. Psychosocial functioning in people with epilepsy in remission and the outcomes of antiepileptic drug withdrawal. PhD thesis: University of Newcastle upon Tyne, UK, 1995.

92. Boylan LS, Flint LA, Labovitz DL. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* 2004;62:258-261.

93. Gilliam FG, Fessler AJ, Baker G, Vahle V, Carter J, Attarian H. Systematic screening allows reduction of adverse antiepileptic drug effects: A randomized trial. *Neurology* 2004;62:23-27.

94. Hessen E, Lossius MI, Reinvang I, Gjerstad L. Slight improvement in mood and irritability after antiepileptic drug withdrawal: A controlled study in patients on monotherapy. *Epilepsy & Behavior* 2007;10:449-455.

95. Giovagnoli AR, Avanzini G. Quality of life and memory performance in patients with temporal lobe epilepsy. *Acta Neurol Scand* 2000;101:295-300.

96. Andelman F, Fried I, Neufeld MY. Quality of life self-assessment as a function of lateralization of lesion in candidates for epilepsy surgery. *Epilepsia* 2001;42:549-555.

97. Kanner AM, Barry JJ. The impact of mood disorders in neurological diseases: should neurologists be concerned? *Epilepsy & Behavior* 2003;4:S3-S13.

98. Ettinger A, Reed M, Cramer J. Depression and comorbidity in community-based patients with epilepsy or asthma. *Neurology* 2004;63:1008-1014.

99. Johnson EK, Jones JE, Seidenberg M. The relative impact of Anxiety, Depression, and Clinical Seizure Features on Health-related Quality of Life in Epilepsy. *Epilepsia* 2004;45:544-550.

100. Loring DW, Meador KJ, Lee GP. Determinants of quality of life in epilepsy. *Epilepsy & Behavior* 2004;5:976-980.

101. Kobau R, Gilliam F, Thurman DJ. Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: Results from the 2004 Healthstyles Survey. *Epilepsia* 2006;47:1915-1921.

102. Mensah SA, Beavis JM, Thapar AK, Kerr M. The presence and clinical implications of depression in a community population of adults with epilepsy. *Epilepsy & Behavior* 2006;8:213-219.

103. Mensah SA, Beavis JM, Thapar AK, Kerr MP. A community study of the presence of anxiety disorder in people with epilepsy. *Epilepsy & Behavior* 2007;11:118-124.

104. Zeber JE, Copeland LA, Amuan M, Cramer JA, Pugh MJ. The role of comorbid psychiatric conditions in health status in epilepsy. *Epilepsy & Behavior* 2007;10:539-546.

105. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. *Acta Neurol Scand* 2004;110:207-220.

106. Gilliam F, Kanner AM. Treatment of depressive disorders in epilepsy patients. *Epilepsy & Behavior* 2002;3:2-9.

107. Tracy JI, Dechant V, Sperling MR, Cho R, Glosser D. The association of mood with quality of life ratings in epilepsy. *Neurology* 2007;68:1101-1107.

108. Attarian H, Vahle V, Carter J, Hykes E, Gilliam F. Relationship between depression and intractability of seizures. *Epilepsy & Behavior* 2003;4:298-301.

109. Perrine K, Herman BP, Meador K. The relationship of neuropsychological functioning to quality of life in epilepsy. *Arch Neurol* 1995;52:997-1003.

110. Bazil CW. Epilepsy and sleep disturbance. *Epilepsy & Behavior* 2003;4:S39-S45.

111. Alanis-Guevara I, Pena E, Corona T, Lopez-Ayala T, Lopez-Meza E, Lopez-Gomez M. Sleep disturbances, socioeconomic status, and seizure control as main predictors of quality of life in epilepsy. *Epilepsy & Behavior* 2005;7:481-485.

112. Pulsipher DT, Seidenberg M, Jones J, Hermann B. Quality of life and comorbid medical and psychiatric conditions in temporal lobe epilepsy. *Epilepsy & Behavior* 2006;9:510-514.

113. Jacoby A, Wang W, Dang Vu T *et al.* Meanings of epilepsy in its sociocultural context and implications for stigma: Findings from ethnographic studies in local communities in China and Vietnam. *Epilepsy & Behavior*, in press.

114. Scambler G, Hopkins A. Being epileptic: coming to terms with stigma. *Sociology of Health and Illness* 1986;8:26-43.

115. Scambler G. Epilepsy. London: Tavistock, 1989.

116. Jacoby A, Gorry J, Gamble C, Baker GA. Public knowledge, private grief: A study of public attitudes to epilepsy in the United Kingdom and implications for stigma. *Epilepsia* 2004;45:1405-1415.

117. Jacoby A. Felt versus enacted stigma: a concept revisited. Evidence from a study of people with epilepsy in remission. *Soc Sci Med* 1994;38:269-274.

118. Baker GA, Brooks J, Buck D, Jacoby A. The stigma of epilepsy: A European perspective. *Epilepsia* 1999;41:98-104.

119. Suurmeijer TPBM, Reuvekamp MF, Aldenkamp BP. Social functioning, psychological functioning, and quality of life in epilepsy. *Epilepsia* 2001;42:1160-1168.

120. DiIorio C, Shafer PO, Letz R, Henry TR, Schomer DL, Yeager K. Behavioral, social, and affective factors associated with self-efficacy for self-management among people with epilepsy. *Epilepsy & Behavior* 2006;9:158-163.

121. Oyegbile TO, Dow C, Jones J *et al.* The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology* 2004;62:1736-1742.

122. Wakamoto H, Nagao H, Hayashi M, Morimoto T. Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan. *Brain & Development* 2000;22:246-255.

123. Amir M, Roziner I, Knoll A, Neufeld MY. Self-efficacy and social support as mediators in the relation between disease severity and quality of life in patients with epilepsy. *Epilepsia* 1999;40:216-224.

124. Gramstad A, Iversen E, Engelsen BA. The impact of affectivity dispositions, self-efficacy and locus of control on psychosocial adjustment in patients with epilepsy. *Epilepsy Res* 2001;46:53-61.

125. DiIorio C, Hennessy M. Epilepsy Self-Management: A Test of a Theoretical Model. *Nurs Res* 1996;45:211-217.

126. Pais-Ribeiro J, da Silva AM, Meneses RF, Falco C. Relationship between optimism, disease variables, and health perception and quality of life in individuals with epilepsy. *Epilepsy & Behavior* 2007;11:33-38.

127. Giovagnoli AR, Meneses RF, da Silva AM. The contribution of spirituality to quality of life in focal epilepsy. *Epilepsy & Behavior* 2006;9:133-139.

128. World Health Organisation Quality of Life Group. What quality of life? World Health Organisation quality of life assessment. *World Health Forum* 1996;17:354-356.

129. Jalava M, Sillanpaa M. Concurrent illnesses in adults with childhood-onset epilepsy: a population based 35 year follow up study. *Epilepsia* 1996;37:1155-1163.

130. Jalava M, Sillanpaa M. Reproductive activity and offspring health of young adults with childhood-onset epilepsy: a controlled study. *Epilepsia* 1997;38:532-540.

131. Jalava M, Sillanpaa M, Camfield C, Camfield P. Social adjustment and competence 35 years after onset of childhood epilepsy: a prospective controlled study. *Epilepsia* 1997;38:708-715.

132. Jalava M, Sillanpaa M. Physical activity, health related fitness and health experience in adults with childhood-onset epilepsy: a controlled study. *Epilepsia* 1997;38:424-429.

133. Shackleton DP, Trenite DGAK, de Craen AJM, Vandenbroucke JP, Westendorp RGJ. Living with epilepsy - Long-term prognosis and psychosocial outcomes. *Neurology* 2003;61:64-70.

134. Bury M. The sociology of chronic illness: a review of research and prospects. *Sociology of Health and Illness* 1991;13, 4:451-468.

135. Robinson I. Personal narratives, social careers and medical courses: Analysing life trajectories in autobiographies of people with multiple sclerosis. *Social Science & Medicine* 1990;30:1173-1186.

136. Weiner CL. The burden of rheumatoid arthritis: tolerating the uncertainty. *Soc Sci Med* 1975;9:97-104.

137. Bury M. Chronic illness as biographical disruption. *Sociology of Health and Illness* 1982;4, 2:167-182.

138. Williams SJ. Chronic illness as biographical disruption or biographical disruption as chronic illness? Reflections on a core concept. *Sociology of Health & Illness* 2000;22:40-67.

139. Charmaz K. Loss of self: a fundamental form of suffering in the chronically ill. *Sociology of Health and Illness* 1983;5:168-197.

140. Link BG. Understanding Labeling Effects in the Area of Mental-Disorders - An Assessment of the Effects of Expectations of Rejection. *Am Sociol Rev* 1987;52:96-112.

141. Jacoby A. Stigma, epilepsy, and quality of life. *Epilepsy & Behavior* 2002;3:S10-S20.

142. Scambler G, Hopkins A. Accommodating epilepsy in families. In: Anderson R, Bury M, eds. Living with chronic illness: the experience of patients and their families. London: Unwin Hyman, 1988.

143. Williams G. The genesis of chronic illness: narrative re-construction. *Sociology of Health and Illness* 1984;6, 2:175-200.

144. Ormel J, Lindenberg S, Steverink N, Vonkorff M. Quality of life and social production functions: a framework for understanding health effects. *Soc Sci Med* 1997;45:1051-1063.

145. Lindenberg S, Frey BS. Alternatives, Frames, and Relative Prices: A Broader View of Rational Choice Theory. *Acta Sociol* 1993;36:191-205.

146. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol* 2007;62:375-381.

147. Berg AT, Vickrey BG. Outcome Measures. In: J Engel JaTAP, ed. Epilepsy: A Comprehensive Textbook. Philadelphia: Lippincott-Raven, 1998:1891.

148. Helde G, Bovim G, Brathen G, Brodtkorb E. A structured, nurse-led intervention program improves quality of life in patients with epilepsy: A randomized, controlled trial. *Epilepsy & Behavior* 2005;7:451-457.